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Research Article

The perioperative course and anesthetic challenge for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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KEYWORDS

Cytoreductive surgery (CRS);
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Abstract *Background:* Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) by the closed technique provide a promising therapeutic option for highly selected patients with peritoneal carcinomatosis. CRS with HIPEC is a long and complex procedure with significant blood and fluid loss, hemodynamic, hematological, and metabolic alterations in the perioperative period, with resultant morbidity and mortality. This work was done to evaluate our early experience in anesthesia and early postoperative care for these cases.

Patients and methods: This retrospective study was done on 13 patients for CRS and HIPEC, with intraoperative and early postoperative recording and evaluation of the fluid and blood losses and replacement, changes in hemodynamic, metabolic, and respiratory parameters and any complications happened.

Results: Our data demonstrated high fluid and blood losses during CRS. During HIPEC, raised body temperature, increased central venous pressure and airway pressure, increased arterial partial carbon dioxide tension ($PaCO_2$), decreased ratio of arterial oxygen partial pressure/fractional inspired oxygen (P_aO_2/F_iO_2), and increased serum lactate were recorded. These were associated with hemodynamic, metabolic, and respiratory acidosis. The patients were continuing resuscitation and correction of any derangements in intensive care unit.

Conclusion: CRS and HIPEC have become standard treatment for certain peritoneal surface malignancies. This extended surgery is considered a challenge for the anesthetist. It is associated with

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relevant fluid, blood, and protein losses, together with hemodynamic, respiratory, and metabolic derangements. However, these derangements are short lived and could be controlled by continuous monitoring and rapid intervention.

1. Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) provide a promising therapeutic option for highly selected patients with peritoneal carcinomatosis arising from different malignancies such as colorectal cancer, gastric cancer, ovarian cancer, or peritoneal mesothelioma with improvement of both patient survival and quality of life [1].

In this technique, the chemotherapeutic agent is typically perfused within the abdominal cavity for 90 min at a temperature of 42 °C, achieving high peritoneal concentrations with limited systemic absorption [2].

CRS with HIPEC is a long and complex procedure with significant blood and fluid loss during debulking, hemodynamic, hematological, and metabolic alterations before and during the HIPEC phase, and even in the early postoperative period, with resultant significant morbidity and mortality [3–5]. For the safety of the patient, both the surgeon and the anesthetist should understand these profound effects with this procedure and how to deal with, to achieve better outcome.

The aim of this work is to study, understand, and evaluate the intraoperative and early postoperative effects of CRS and HIPEC on hemodynamic, hematological, metabolic, and respiratory functions and perioperative fluid and blood losses and replacement. Also, assessment of the perioperative treatment related morbidity and mortality to improve the intraoperative and postoperative outcome of this treatment strategy.

2. Methods

This retrospective study was done on patients with CRS and HIPEC with a standard closed technique, done in the Department of Surgery of the National Cancer Institute, Cairo University between March 2010 and January 2011. After the approval of the local ethics committee of National Cancer Institute, Cairo University, data were collected from anesthesia and ICU sheets, and the study was done on 13 patients, ASA physical status class I and II patients.

Two hours prior to induction of general anesthesia Ranitidine 150 mg was given, and then, antibiotic and Ondansetron 4 mg were given intravenously before induction. Another dose of antibiotic was given with starting HIPEC phase.

Standard monitoring of the patients with electrocardiogram, capnography, and pulse oximetry was started. Anesthesia was induced intravenously, after volume preload, with fentanyl 3–5 μg kg^{-1} and Propofol 2–3 mg kg^{-1} given intravenously, and intubation was facilitated with Atracurium 0.5 mg kg^{-1}. Ventilation was controlled; anesthesia was maintained with Sevoflurane in oxygen, maintenance shot doses of relaxant and supplemented with either intravenous Morphine 10 mg and fentanyl 50–100 μg shots, or epidural marcaine 0.25% 10–15 ml bolus and 5 ml shot doses throughout the surgery. Large-bored intravenous cannulas, an arterial cannula, central venous line, and a urinary catheter were then applied.

Continuous monitoring of invasive arterial blood pressure, central venous pressure, core temperature by an esophageal probe placed at the middle third of the esophagus, airway pressure, and urinary output were started.

Observation and recording of changes in pulse rate, mean arterial blood pressure, airway pressure, central venous pressure (CVP), urine output, ascetic fluid drainage, and blood loss were started from the start of surgery. Signs of volume loss were treated by intravenous (i.v.) crystalloids, colloids, blood and fresh frozen plasma, or vasoactive drugs to keep mean arterial pressure above 60 mmHg and within 20% of baseline values.

The heated chemotherapy was perfused with a closed abdomen technique, taking from 60 to 90 min., the abdomen is closed at the skin level and the Tenckhoff catheter, and suction drains and temperature probes exit through the abdominal wound. A roller pump forces the heated chemotherapy solution into the abdomen through the inflow catheter and pushes it out through the outflow catheter. The chemotherapeutic was chosen according to the type of tumor, which was Cisplatin for ovarian carcinoma and Mitomycin for colorectal carcinoma and pseudomyxoma peritonei. A heat exchanger which keeps the fluid being infused at 44–46 °C, so that the intraperitoneal fluid temperature was maintained at 42–43 °C. Following the heated infusion, the surgeon performed the anastomoses and reconstructive procedures.

Arterial blood samples were collected for full blood count, blood gas analysis, electrolytes, and glucose during resection to assess the patient condition and correct any abnormalities 15 min before the HIPEC procedure. Measurements done before HIPEC included the following: heart rate, mean arterial pressure, central venous pressure end tidal CO_2, airway pressure, urinary output, core temperature, and arterial blood gases. Other recordings were done 30 min after starting chemotherapy infusion and 15 min after the end of the procedure. During the HIPEC procedure, the urinary output was recorded every 15 min, intravenous fluids increased to about 1000–1500 ml/h, together with or without an IV dose of dopamine (3 μg/kg/min) aiming to keep urinary output at more than 100 ml every 15 min. Any intraoperative complication was recorded.

With good replacement, general surgical condition and hemostasis, and accepted blood gases and vital signs, extubation was done in the theater, or the patient was shifted and intubated to continue mechanical ventilation in the intensive care unit (ICU) till correction and stabilization of vital signs. All patients were shifted to ICU and monitoring is continued with recording of wound and nasogastric tube drainage. Complete blood investigations were done including complete blood picture, liver functions, renal functions, electrolytes, coagulation profile, arterial blood gases analysis, and chest X-ray upon patient arrival. Correction of any derangements, replacement, inotropic support, and ventilatory support started according to the patient condition, urine output, and amount of drained fluids from the wound and from nasogastric tube

drainage. Prophylactic antibiotic coverage, prophylactic low molecular weight heparin, and prophylactic antiulcer measures started in all patients if no contraindication existed.

Quantitative data were expressed as range and/or mean ± standard deviation (SD). Paired Student's *t*-tests or two-way analysis of variance (ANOVA) test was used for variable differences in groups, and Bonferroni correction tests were used for correction of multiple comparisons. P value < 0.05 was considered statistically significant and P value > 0.05 was considered nonsignificant.

3. Results

From March 2011 to January 2012, combined CRS and HIPEC were done for 13 patients for the management of peritoneal carcinomatosis. Patients' characteristics, primary diagnosis, and operation time are summarized in Table 1.

3.1. Intraoperative data

The crystalloid and colloid intake, blood and fresh frozen plasma transfused, estimated blood loss, and urine output are recorded for all patients during surgery in Table 2. Also, a number of patients who received potassium infusion, vasoactive drugs to manage hypotension, epidural analgesia, and dopamine infusion were recorded.

The changes recorded before, during, and after HIPEC procedure in temperature, hemodynamic changes, acid–base, oxygenation, gas exchange, airway pressure, and CVP in 12 patients (one patient not included) are illustrated in Fig. 1A–I.

There was a progressive nonsignificant decrease in pH before, during and after HIPEC than baseline, and a significant decrease in bicarbonate levels before, during, and after HIPEC (18.3 ± 2.3, 17.5 ± 2.1, and 16.3 ± 1.9 mmol l^{-1}, respectively) than the baseline measurements (25.7 ± 1.1 mmol l^{-1}) was recorded. Serum lactate levels, measured after HIPEC, were significantly increased than before HIPEC (4.7 ± 2.2 mmol l^{-1} and 1.7 ± 1.2 mmol l^{-1}, respectively). The core temperature was significantly decreased after the cytoreductive surgery and before HIPEC than the baseline (33.5 ± 1.7 °C and 36.5 ± 0.6 °C, respectively) then significantly increased during HIPEC (38.2 ± 1.1 °C) and persisted after completion (38 ± 0.8 °C) than before this phase.

PaCO2 was increased significantly during the HIPEC than before (from a mean of 32.7 ± 3.5 to 39.4 ± 2.5 mmHg) then decreased again after HIPEC to 37.8 ± 2.2 mmHg, which is still significantly increased than before HIPEC. Tissue oxygenation was also affected, with significant *decrease in the* P_aO_2/F_iO_2 (from 361 ± 44.8 before to 196 ± 29.1 during HIPEC), to increase again after completion of HIPEC to 240 ± 34.2.

With abdominal closure during HIPEC, there is a concomitant significant increase in airway pressure than before closure (26.3 ± 3.6 vs 17.5 ± 2.1 cm H_2O) and central venous pressure (12.25 ± 2.2 vs 8.5 ± 1.2 cm H_2O). Then, after completion of HIPEC and abdominal opening, the airway pressure and CVP decreased significantly than during the HIPEC (18.6 ± 2.3 cm H_2O and 9.5 ± 1.4 cm H_2O, respectively) but without significant changes from baseline and before HIPEC.

Regarding hemodynamic changes, there was significant increase in heart rate during CRS before HIPEC than the baseline readings (77.4 ± 14.2 vs 70.4 ± 8.1 beat/min) and also significantly increased more during HIPEC (94 ± 12 beat/min), which decreased after HIPEC (85.6 ± 11.5 bpm) but still significantly increased than baseline and before HIPEC. Mean arterial pressure decreased significantly before |HIPEC than baseline (84.3 ± 9.2 vs 89.1 ± 11.1 mmHg) and decreased significantly more during chemotherapeutic infusion (75 ± 9.3 mmHg) then significantly increased again after completion of the procedure than during HIPEC (81.2 ± 11 mmHg), but still significantly less than baseline.

No intraoperative patient mortality and intraoperative complications are listed in Table 3. The HIPEC phase was done to all patients except for one case.

3.2. Postoperative data

All the patients were shifted to the ICU; seven of them were intubated, and five patients were on inotropic support. The early postoperative patients' data in ICU, in day 0 (the period from end of the operation until start of first postoperative day), which is 8.2 ± 2.5 h, day 1, and day 2 are listed in Table 4.

Compared to baseline records, there was persistent significant decrease in Hb in day 0 than baseline (11.5 dl^{-1}). Also, there was persistent significant decreased bicarbonate, increased serum lactates, with decreased pH in day 0 than baseline, and was not significantly different in the following days. Significant increased INR (international normalized ratio) in days 0 and 1 than baseline (1.1 ± 0.12) was normalized in 3 days except with patients with impairment of liver enzymes. There was significant decrease in mean albumin level) in days 0, 1, and 2 compared to baseline records (3.5 ± 0.61 g/dl).

Table 1 Characteristics of 13 patients undergoing CRS and HIPEC. Data are expressed as number and mean ± SD.

Sex Male	6
Female (number)	7
Age (years)	50.2 ± 7.5
Weight (kg)	67 ± 8.6
Height (c)	156 ± 7.8
ASA 1	9
ASAII (number)	4
Primary diagnosis (number)	Ovarian cancer: 4 Pseudomyxoma Peritonii: 4 Peritoneal, colorectal carcinomatosis: 5
Total time of operation (h)	8.45 ± 2.7
Time of surgery (h)	7.30 ± 1.8

"American Society of Anesthesiologists Grade" (ASA).

Table 2 Intraoperative fluids and blood products, urine output, potassium, dopamine and inotrope infusion, and epidural analgesia of 13 patients.

	Mean ± SD	Range	Number of patients (total: 13)
Total crystalloid (ml)	7571.4 ± 4004	5000–15,000	13
Total colloid (ml)	1714 ± 1219	500–4000	13
Red blood cells (units)	5.7 ± 3.3	2–10	13
Fresh frozen plasma (units)	6 ± 3.7	2–10	12
Estimated blood loss (ml)	3400 ± 1622	1300–5000	13
Albumin 25% (ml)	157.3 ± 53	100–200	7
Total urine output (ml)	3880 ± 402	3200–4500	13
Urine output during HIPEC (ml)	1283 ± 248	1000–1500	13
Potassium infusion		20 meq/h	8
Dopamine infusion (μg/kg)		3 μg/kg/min	9
Inotrope infusion (adrenaline or noradrenaline)			5
Epidural analgesia (ml/h)	5 ± 2.3 ml/h	5–8 ml/h	5

Early postoperative complications in ICU including hemodynamic complications, chest related complications, liver impairment, kidney impairment, and the number of patients died in ICU are listed in Table 5.

4. Discussion

This study presents our early experience with CRS and HIPEC. It includes anesthetic considerations, intraoperative events and derangements with their management, and the early postoperative course in the ICU with reference to the morbidity and mortality. Closed technique was used to achieve and maintain hyperthermia with minimal heat loss and with minimal contact or aerosolized exposure of the operating room staff to the chemotherapy. Tumoricidal activity is achieved at 41–43 °C; that in-flow temperature usually exceeds 45 °C [1,6].

CRS and HIPEC are complex lengthy procedures involving exploratory laparotomy, extensive peritoneal and multivisceral resection, abdominal closure, then perfusion of high-dose of intraperitoneal hyperthermic chemotherapy, and performing a number of anastomoses. This complex surgical procedure was associated with significant fluid loss, fluid shift, blood loss, and protein loss with the hyperthermic chemotherapy [3,4].

In our study, infusions with crystalloids, colloids, fresh frozen plasma, albumin, and blood were guided by continuous monitoring of pulse, blood pressure, central venous pressure, serum electrolytes, hemoglobin, and urine output. The infusion rate was high during resection stage, to restore normovolemia, cardiovascular system stability, and correction of electrolytes before HIPEC, and was high during HIPEC to maintain good perfusion pressure, to maintain good urine output and to compensate for vasodilatation caused by the heated chemotherapy and the increased intraabdominal pressure. Adequate urine output (0.5–1 ml/kg/h) and CVP (6–8 mm H_2O) were our aim, which sometimes need IV Furosemide to avoid tissue edema that was crucial for safe anastomoses (usually requested by the surgeon). Red blood cell transfusion was necessary to all patients intraoperatively, and also, fresh frozen plasma was transfused for clinical evident bleeding to compensate for coagulation factor defect.

Nguyen and Wolfe in 2005 reported that adequate fluid therapy and blood replacement play a major role in the maintenance of adequate systemic and regional perfusion and prevent systemic hemodynamic disorders, that is, a critical factor when the blood volume is low [7]. Other studies reported that blood loss was due to surgery and disturbance of coagulation with an increased INR and fall in AT III values, as well as prolonged aPTT and a reduced number of platelets. Additionally, coagulation could be abnormal due to lower values of coagulation factors not measured with standard tests, such as factor XIII [3,7,8]. Significant risk factors necessitating intraoperative blood transfusion in CRS were studied by other authors; the most important were operative length more than 9 h, preoperative INR more than 1.2, preoperative hemoglobin less than 125 g/l, and peritoneal cancer index C 16 [9].

Esophageal temperature was continuously measured throughout the study. Although hypothermia during CRS was controlled by forced air warming with blankets and warmed fluid infusions, all the patients were hypothermic before the HIPEC. This can be explained by the large amount and rapid rate of infusions together with the large surface area exposed for long time. Then, the temperature started to increase with infusion of the hyperthermic solution during and after finishing the HIPEC procedure. The body temperature rise was controlled by stopping of the heating measures used during surgery, cold and rapid infusions, and the cooling measures of the skin. This agrees with Kanakoudis in 1996, who found the core body temperature during the hyperthermic perfusion period increased significantly but remained within clinically acceptable values [10]. In other study during chemotherapeutic perfusion, there were significant increases in mean temperature, and despite the intensive cooling measures, 18% of patients had an increase in core temperature greater than 39 °C [4].

Hemodynamically, our patients had significant increase in heart rate and decrease in mean arterial pressure with CRS; this can be due to blood loss, fluid loss, and hypothermia. Tachycardia and hypotension increased more with abdominal closure and infusion of the heated chemotherapy due to rise of body temperature and decreased systemic vascular resistance. As it was found that, during HIPEC, the increased body temperature results in corresponding increase in metabolic rate, the patients developed hyperdynamic circulation with increase in heart rate and in end tidal carbon dioxide values, with metabolic acidosis and elevated lactate levels [3,4,10].

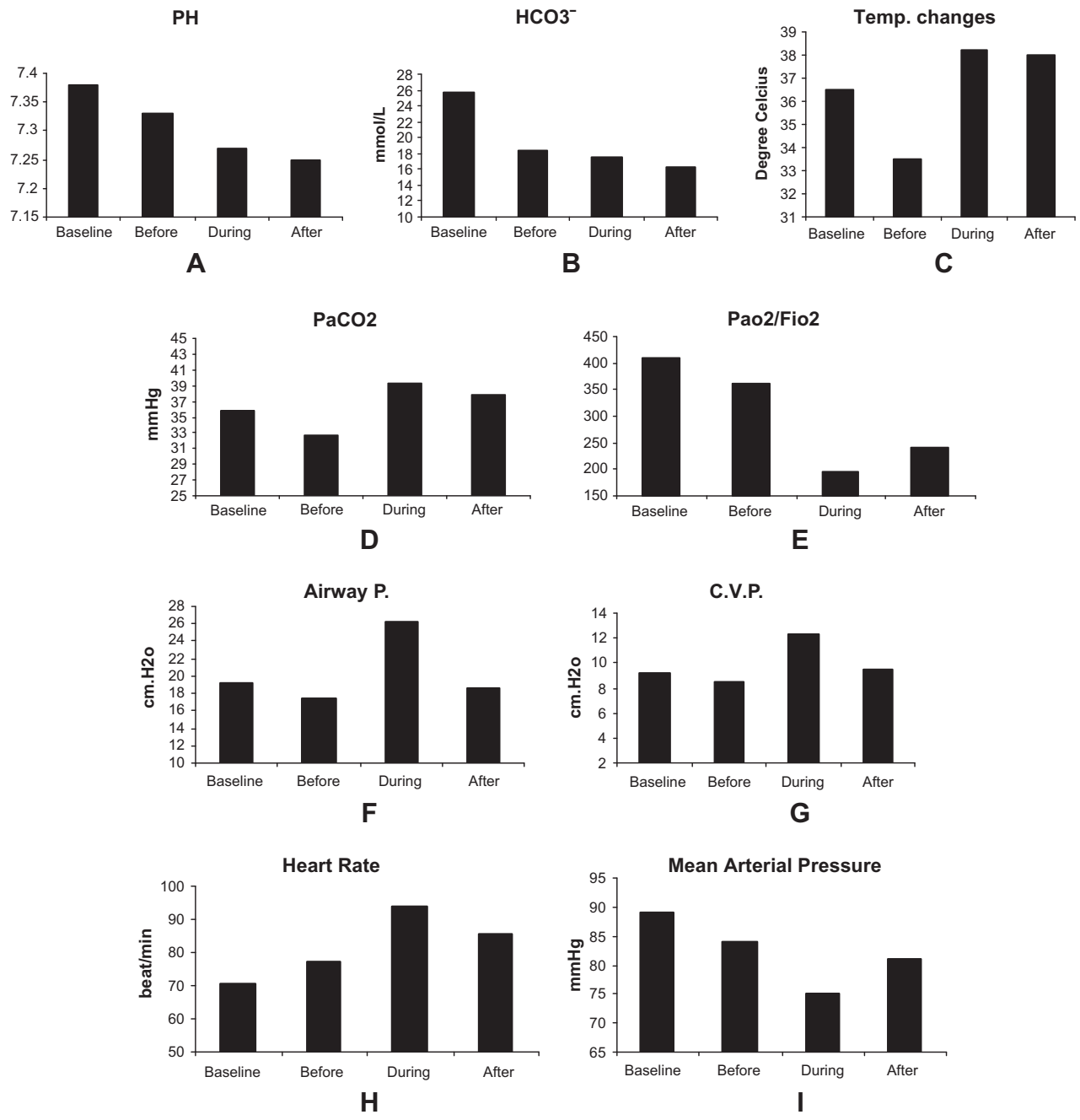

Figure 1 Intraoperative hemodynamic and metabolic changes, airway pressure, and central venous pressure (CVP) of 12 patients before, during, and after HIPEC compared to baseline.

Table 3 Intraoperative complications of 13 patients.

Intraoperative complication	Number of patients (total: 13)
Blood loss (> 10% of blood volume)	13
Hypotension (> 20% decrease in mean arterial pressure)	9
Hypokalemia < 3 meq/L	6
Metabolic acidosis	13
Diaphragmatic tear	4
Temperature > 38.5 °C	2
Pulmonary edema	1

Hypotension necessitating vasoactive drug infusion started for hemodynamic support in four patients during HIPEC and continued postoperatively then weaned in ICU thereafter. These hemodynamic and cardiac function changes during HIPEC were also reported in other studies with increased heart rate, decreased arterial pressure, increased cardiac output, and decreased systemic vascular resistance. These effects were explained to be due to the reduction in the venous return by narrowing of the vena cava associated with a reduction in the abdominal blood volume and an increase in splanchnic vascular resistance [3,4,8,11–13].

The development of combined metabolic and respiratory acidosis in all patients of the study was recorded, which

Table 4 Patients' progress in the early postoperative period in ICU.

	Day 0	Day 1	Day 2
Hemoglobin (g dl^{-1})	7.8 ± 1.3*	10.2 ± 1.2	10.5 ± 1.8
Platelet count (10^9 $l^{-1)}$	148.7 ± 67	162.2 ± 77	165 ± 58.6
White blood cells	8.6 ± 4.8	12.6 ± 6.8	9.5 ± 2.8
Temperature (°C)	37.3 ± 0.4	37.7 ± 0.6	37.9 ± 0.6
INR	1.8 ± 0.53*	1.5 ± 0.45*	1.3 ± 0.68
Fibrinogen (g/L)	236 ± 220	539 ± 450	654 ± 622
pH	7.28 ± 0.1*	7.38 ± 0.06	7.39 ± 0.11
HCO_3 (mmol l^{-1})	18.3 ± 3.8*	26 ± 3.5	26.5 ± 1.3
Lactate (mmol l^{-1})	5.2 ± 2.5*	3.2 ± 1.3	2.5 ± 1.1
Albumin (g/dl)	2.1 ± 0.7*	2.4 ± 0.5*	2.8 ± 0.8*
IV fluids (ml/h)	192 ± 45	167 ± 44	150 ± 32
Drains (ml/day)	483 ± 220	688 ± 223	520 ± 170
Nasogastric tube drainage (ml/day)	167 ± 172	300 ± 76	240 ± 66
Urine output (ml/day)	857 ± 254	1820 ± 455	1552 ± 370

* $p < 0.05$ compared to baseline value.

Table 5 Early postoperative complication.

Type of complication	Number of patients (total 13)
Inotropic support	4
Tachycardia	11
Arrhythmia	1
Heart failure	1
Fever	12
Reintubation and ventilation	2
Pneumonia	3
Pulmonary embolism	1
Pleural effusion	3
Renal impairment	0
Liver impairment	7
intestinal leak	1
Platelet dysfunction	0
Death	2

appears to be mainly metabolic. Metabolic acidosis in most of the cases started before the start of HIPEC procedure and increased more during and after the hyperthermic perfusion with a significant decrease in bicarbonate and increased lactate levels. This was explained by hypothermia, hypotension, fluid losses, blood loss, and increased intraabdominal pressure. No bicarbonate infusion was given except in one case, after pH reached 7.14 during hyperthermic perfusion. Also, gas exchange was impaired with significant increase in $PaCO_2$ due to the hypermetabolic state. This was observed by other centers, with development of both metabolic and respiratory acidosis with persistent mild metabolic acidosis after completion of the procedure [3–5,14].

In this study, we observed significant increases in central venous pressures, airway pressure, $PaCO_2$, and a significant decrease in P_aO_2/F_iO_2 during and after HIPEC. It was also found in other studies using closed abdomen technique, an increase in intraabdominal pressure, together with shift of the diaphragm resulting in an increase in airway pressure and a reduction in the functional residual capacity. These changes lead to rise in the central venous pressure, decreased lung volume, a decrease in the oxygenation ratio, together with hyperdynamic circulation during HIPEC characterized by increase in end tidal carbon dioxide values and increased systemic oxygen demand [3,10,15–17]. Shime et al. found an increased oxygen consumption and a slight rise in oxygen extraction due to hyperthermic metabolic conditions during HIPEC [11].

All the patients in the study received potent antiemetic preoperatively to control the emetic effect of chemotherapy. Intraperitoneal chemotherapy complications include those linked to the drug administered; Cisplatin administration results in nausea, vomiting, and renal toxicity which was avoided by effective antiemetic drugs and suitable i.v. hyperhydration considering the systemic exposure to the agent after intraperitoneal application [18,19].

With the start of chemotherapeutic infusion, increased fluid infusion and dopamine infusion 3 μg/kg started in 9 patients, with a maintained urine output during HIPEC procedure reaching 1000–1500 ml/h. During HIPEC, adequate urine output is mandatory and is considered a reflection of good kidney perfusion, especially during the periods of increased intraabdominal pressure, heated chemotherapeutic infusion with its concomitant peripheral vasodilatation, and as a protective from renal toxicity [3,18].

Intraoperative pain was controlled by intravenous fentanyl and morphine or by combined epidural infusion of local anesthetic and fentanyl, and it was found that pain control by any of the two ways was not related to postoperative ventilation. Other studies have reported that patients receiving epidural analgesia required less postoperative mechanical ventilation, while others postulated that cytoreductive surgery and HIPEC can be achieved with or without epidural analgesia [3,4].

There was no intraoperative mortality, and only one patient suffered from severe hypotension due to severe bleeding, which was not controlled by vasoactive drugs, and the HIPEC procedure could not be done. The intraoperative complications of HIPEC which was recorded in all patients were bleeding, extensive fluid loss, and metabolic acidosis. Five patients developed hypotension necessitating inotropic support, and four patients had diaphragmatic tear with intraoperative chest tube insertion. One patient had pulmonary edema with decrease in oxygen saturation during surgical resection which may be due to rapid infusion and low albumin level that was controlled by frusemide and positive pressure ventilation and later albumin infusion.

5. Postoperative management

All the patients in the study were shifted to ICU for stabilization of hemodynamic and ventilation, correction of acid–base, and assessment of organ functions. This was reported in other studies that postoperatively, most patients should be transferred to the ICU, as postoperative fluid loss during the first 72 h following surgery is still very high. In other studies, patients were transferred either to the post-anesthesia care unit (PACU) or to intensive care unit (ICU) depending on their overall status [3–5].

The average length of stay in ICU was 4.4 days (range of 2–10 days). Seven patients admitted and intubated to continue mechanical ventilation; four of them because of intraoperative diaphragmatic tear, and the rest with unstabilized hemodynamics or ventilation. All the patients were extubated in the early morning of the first day except two patients were extubated on the second day after stabilization of the general condition and correction of gas exchange and oxygenation.

On day 0, blood pressure was stable except for four patients who were controlled by intravenous inotropic drug infusions, blood transfusion, and fluid intake; and weaning was complete on the first day. Tachycardia was present in most of the patients ($n = 10$), which was stabilized on the first day by stabilization of the hemodynamic and metabolic parameters, fluid intake and blood transfusion, pain control, and control of increased temperature. One patient developed atrial fibrillation, another one developed left sided heart failure, and both were managed according to their condition.

Liberal intravenous fluid intake, crystalloid and colloid, was guided by hemodynamic changes, CVP, serum electrolytes, urine output, and amount of fluid losses from drains and nasogastric tube. Blood transfusion was mostly given on day 0 ($n = 8$) together with fresh frozen plasma guided by the drains, hemoglobin percent and hematocrit value, and coagulation profile. Also, there were significantly decreased albumin levels, which started to fall during surgery and remained low postoperatively. Albumin was given to all patients to keep serum albumin above 3.0 g/dl and to compensate for fluid losses and excess abdominal fluid rich protein drained.

Postoperative fluid losses via the drains and the nasogastric tube drainage were very high in day 0 and day 1 in ICU and then decreased gradually with the next days. In other studies, the daily amount of fluid collected by drains decreased progressively from the 1st to the 7th postoperative day, and the daily fluid output of the nasogastric tube was close to 1000 ml/24 h until day 6 [20]. Schmidit et al. in 2008 reported that fluid loss during the first postoperative 72 h averaged 5.7 l/day, and 42% of fluid losses came from abdominal drains [3].

Temperature increased in all patients on the first and second days (mean of 37.7° and 37.9°) and started to normalize after that except for 2 patients, which continued with fever with starting pneumonia. In addition, the fibrinogen level was elevated from the first postoperative day and continued elevation in the ICU stay time. Baratti et al. (2010) reported that the temperature was close to 38° during the first 10 postoperative days, in the absence of sepsis. Together with the high temperature, a gradual and marked increase in the fibrinogen level with marked digestive hypersecretion, which were considered the manifestations of the high-inflammatory syndrome following HIPEC [3,20].

All the patients were admitted to ICU with decreased bicarbonate level, high serum lactate level, and metabolic acidosis, which were normalized by day 1 due to stabilization of the hemodynamics, normalization of temperature, and fluid and blood replacement.

Continuous monitoring for our study patients for any chest complication was done; good prophylactic antibiotic coverage was given; and chest physiotherapy was started from day 1 under supervision of physiotherapist with good pain control to prevent lung collapse. Four patients were admitted with chest tube drainage after intraoperative diaphragmatic tear and two patients developed minimal pleural effusion not necessitating drainage. It was explained by Baratti et al. that the inflammatory reactions could be responsible for production of postoperative exudative pleural effusion [20]. Three patients developed pneumonia with resultant hypoxia and fever; two of them were intubated and ventilated. Another patient had ventilation/perfusion scan done with a high probability of pulmonary infarction. A study was done to determine the incidence and severity of thoracic reactions in patients undergoing intraperitoneal heated chemotherapy. Thoracic complications occurred in 86% of the study patients, including atelectasis, pleural effusions, pulmonary edema, pneumonia, and pneumothorax [21].

Different cytostatic agents used for HIPEC can lead to systemic toxicity as bone marrow depression in the form of leucopenia, anemia, thrombocytopenia, heart, liver or renal toxicity, and other side effects [4,22].

In our study, the average hemoglobin percent on admission to ICU ranged 6.9–11.2 g dl^{-1}, which was corrected if needed by blood transfusion to be maintained above 10 g dl^{-1} in the next days. Leukocytic count and platelet count were within normal average limits, without great changes within the patients' stay in ICU. INR was significantly higher than baseline on day 0 due to intraoperative dilution of coagulation factors, which necessitate fresh frozen plasma transfusion in patients with excess uncontrolled ooze. It is normalized gradually within 3 days, except in three cases, that took longer time because of association of liver impairment and high liver enzymes. Yan and his colleagues reported that a low hemoglobin level of 6.5–7.9 g dl^{-1} in 26% upon ICU admission of their patients. This was explained as hemodilution, since patients are given a large volume of intravenous fluid intraoperatively. Also, there were significant decreases in prothrombin time and increase in INR that was normalized within 5 days in 78% of their patients [23].

There were good urine output, no signs of renal failure, or significant changes in kidney functions were observed in any patient in the study. Raft et al. retrospectively analyzed the perioperative care of 20 patients who underwent HIPEC, and there was no renal failure or impact on blood cells counts for 7 days postoperatively [14].

There were more than threefold increases in liver enzymes, elevated bilirubin level, increase in INR, and decrease in prothrombin concentration in seven patients, maximum on the first and second day in ICU then gradually normalized in the next days. Hepatic tests in other studies showed early but moderate cytolysis without cholestasis. Transaminases increased twofold to threefold during the first 4 postoperative days which was explained to be due to extensive electro coagulation of the liver capsule [20].

Pain was controlled either by continuous epidural infusion of marcaine 0.125% and fentanyl, or by intravenous shots of morphine.

Two patients died in ICU; one of them due to liver cell failure and the other due to intestinal perforation and leak.

6. Conclusion

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy has become standard treatment for selected patients with certain peritoneal surface malignancies. This extended surgery is considered a challenge for the anesthetist. It is associated with relevant fluid, blood, and protein losses, together with hemodynamic, respiratory, and metabolic derangements. However, these derangements are short lived, easy to control, and not likely to contribute to morbidity and mortality. Continuous monitoring intraoperatively and postoperatively with rapid interaction with anticipated events is essential. This is together with good understanding of both the surgeon and the anesthetist about these effects and a strong and rapid interaction between them.

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